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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/716,936	11/20/2003	Tod R. Smeal	034536-0220	6791

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/716,936	**Applicant(s)** SMEAL ET AL.	
	Examiner SEAN E. AEDER	**Art Unit** 1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 09 April 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-3, 6-14 and 18-25*.
   Claim(s) withdrawn from consideration: ____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/MISOOK YU/
Primary Examiner, Art Unit 1642

Continuation of 11. does NOT place the application in condition for allowance because: Claims 1-3, 6-14, and 18-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for the reasons stated in the Office Action of 1/9/08 and for the reasons set-forth below. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also Ex parte Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to methods for monitoring every therapeutic effect of a therapeutic composition on any cancer in a mammal comprising measuring phosphorylation of PAK4 on ser-474 in biopsies before and after administration of a therapeutic composition, wherein a lower level of PAK4 phosphorylation on ser-474 in the biopsy after administration of the therapeutic composition, as compared to the level of PAK4 phosphorylation on ser-474 before administration of the therapeutic composition, indicates that the therapeutic composition has every type of therapeutic effect on cancer in said mammal. However, Applicant has not demonstrated that administered therapeutic compositions reduce PAK 4 phosphorylation on ser-474 in subjects.

The specification teaches a phosphospecific anti-PAK4 polyclonal antibody, #108, which was raised against a fragment of PAK4 that was phosphorylated on serine-474 (paragraph 52, in particular). The specification further states that phosphospecific antibodies directed against serine-474 detect activated PAK4 (paragraph 4). The specification further states that "The data for the phosphospecific antibody (#108) in colon carcinomas is especially informative (6 out of 6 patients showed marked perinuclear staining in tumor and not distal benign tissue….This result strongly suggests that PAK4 is specifically active in colon tumor cells and inactive in benign colon tissue from the same patient. Staining of phosphorylated PAK4 was also observed in renal cell carcinoma, lung adenocarcinoma, prostatic adenocarcinoma, intraductal breast adenocarcinoma, and ovarian adenocarcinoma" (paragraph 80). The specification further states: "In tumors, strong staining with phosphospecific-PAK4 antibody was identified in colonic adenocarcinomas (while distal benign tissue failed to show phospho-PAK4 staining). On a scale of 0-3, "0" indicates no staining, "1" is indicative of weak staining, "2" indicates moderate staining and "3" indicates strong staining. Adenomatous epithelium was faintly to moderately positive, but most normal epithelium showed only staining of "1" for phosphorylated PAK4. Prostatic adenocarcinoma showed moderate staining ("2")" (paragraph 81). The specification further states: "In benign tissues, the most prominent staining for phosphorylated PAK4 was seen in adeipocytes, cardiac myocytes, sebaceous glands, and occasional macrophages. Additional positive cell and tissue types included hair follicles, benign prostatic epithelium, breast epithelium, and urothelium" (paragraph 82). However, the specification provides no working examples of the claimed invention. The specification only provides general guidelines or prophetic teaching of how changes in PAK phosphorylation levels could be used to monitor an undisclosed effect of a therapeutic composition (paragraph 9, in particular).
The state of the art is such that if a molecule such as phosphorylated PAK4 is to be used as a surrogate for a particular diseased state, said particular disease state must be identified in some way with phosphorylated PAK4. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. While the teachings of Tockman et al are directed to diagnostics, the teachings of Tockman et al demonstrate the state of the art for predictably using markers to determine any diseased state (such a diseased state of a specific "effect on cancer"). Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence of a particular change in PAK4 phosphorylation on Ser-474 accompanying a particular effect of a therapeutic composition, one of skill in the art would not be able to predictably determine that said particular change in PAK4 phosphorylation on Ser-474 after administration of a composition gives rise to, or is indicative of, a particular effect without undue experimentation.

The level of unpredictability for using a marker, such as PAK4 phosphorylation on Ser-474, as an indicator of any particular disease state, or therapeutic effect, is quite high. Since neither the specification nor the prior art provide evidence of a universal association between the claimed method and any and every effect of a therapeutic composition, a practitioner wishing to practice the claimed invention would be required to provide extensive experimentation to demonstrate such an association. Such experimentation would in itself be inventive.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

In the Submission filed 4/9/08 Applicant amended the claims to recite that the effect is a "therapeutic" effect. Applicant further repeats arguments that have already been addressed. Further, Applicant cites Example 5 of the specification and indicates that Example 5 demonstrates that the level of PAK4 phosphorylation on ser-474 decreases when a particular therapeutic composition is administered to an individual who has colon cancer. Applicant further states that several carcinomas exhibit elevated PAK4 phosphorylation.

The arguments found in the Submission filed 4/9/08 have been carefully considered, but are not deemed persuasive. In regards to the citation of Example 5 and the argument that Example 5 demonstrates that the level of PAK4 phosphorylation on ser-474 decreases when a particular therapeutic composition is administered to an individual who has colon cancer, no such demonstration is presented in Example 5. There has been no demonstration showing that administered compositions that reduce PAK4 phosphorylation on ser-474 result in every or any therapeutic effect. Due to the unpredictability of using a particular biomarker (such as phosphorylation levels of PAK4 on ser-474) as a surrogate for a particular diseased state (such as a particular therapeutic effect), as taught by Tockman et al (see above), one of skill in the art would not predict that the ability of an administered composition to reduce phosphorylation of PAK4 on ser-474 indicates that said composition provides every or any therapeutic effect without such a demonstration..